Diphtheria

REPORT IMMEDIATELY

Section 1: ABOUT THE DISEASE

A. Etiologic Agent

Diphtheria is caused by toxin-producing strains of *Corynebacterium diphtheriae*, a gram-positive, irregularly staining bacterium. Rarely, other *Corynebacterium* species (*C. ulcerans* or *C. psuedotuberculosis*) may produce diphtheria toxin and can cause classic diphtheria. Whether diphtheria bacteria produce toxin depends on infection by a virus bacteriophage carrying the *tox* gene. There are four strains or biotypes of *C. diphtheriae:* gravis, mitis, intermedius, and belfanti. Toxin-producing strains of all biotypes produce an identical exotoxin. There is no consistent difference in pathogenicity or severity of disease among the biotypes; however, the order of their likelihood of producing toxin is: gravis, mitis, intermedius, and belfanti.

B. Clinical Description

Diphtheria has two forms: respiratory and cutaneous. Respiratory (nasal, pharyngeal, tonsillar, and laryngeal) diphtheria is typically caused by toxin-producing (toxigenic) strains of *C. diphtheriae*. Cutaneous disease can be caused by either toxigenic or nontoxigenic strains. The respiratory form of the disease is characterized by the presence of a membrane that is usually visible over the tonsils or the throat. Respiratory diphtheria begins 2–7 days after infection. Initial symptoms of illness include a sore throat and low-grade fever. Swelling of the neck (“bull-neck”) from soft-tissue inflammation can develop and is a sign of severe disease. The membrane may obstruct breathing and can be life threatening. Other complications of diphtheria are caused by systemic effects of the absorbed diphtheria toxin. These complications include myocarditis (inflammation of the heart) and nerve paralysis. The case fatality rate of 5–10% for respiratory diphtheria has changed little in 50 years. The respiratory form of diphtheria usually lasts several days, and complications can persist for months.

Nontoxigenic *C. diphtheriae* can also cause membranous pharyngitis; the disease is usually mild but can lead to bloodstream invasion endocarditis. The isolation of *C. diphtheriae* from the throat does not necessarily indicate a pathogenic role in the illness. Although the frequency with which this occurs is unknown, a small percentage of the population may carry nontoxigenic or toxigenic strains of *C. diphtheriae* without disease symptoms. Respiratory disease caused by nontoxigenic *C. diphtheriae* should be reported as diphtheria. Other pathogens can cause membranes in the respiratory tract, including *Streptococcus* species, Epstein-Barr virus, cytomegalovirus, *Candida,* and anaerobic organisms (Vincent’s angina).

Cutaneous diphtheria, caused by either toxigenic or nontoxigenic strains, is usually mild, typically consisting of non-distinctive sores or shallow ulcers, and only rarely involving toxic complications (1–2% of infections with toxigenic strains). Since 1980, cutaneous diphtheria has not been a nationally reportable disease.

C. Vectors and Reservoirs

Humans are the only host of *C. diphtheriae*.

D. Modes of Transmission

Diphtheria is transmitted from person to person by respiratory droplets or by direct contact with the nasopharyngeal secretions of an infected person. Contact with articles soiled with discharges from cutaneous lesions of infected people can be a source of infection, but this has rarely been documented. Raw milk has served as a vehicle for transmission.

E. Incubation Period

The incubation period is usually 2–7 days, but may occasionally be longer.

F. Period of Communicability or Infectious Period

In untreated persons, the infectious period begins at symptom onset and extends through two weeks after onset in the majority of patients (but may range up to six weeks post onset). If patients are treated with antibiotics, communicability usually lasts less than four days. However, chronic carriage may occur, even after antimicrobial therapy. Patients are considered infectious until 2 successive nose and throat cultures (and cultures of skin lesions in cutaneous diphtheria), obtained $\geq$24 hours apart and at least 24 hours after completion of antimicrobial therapy, are negative. (See Section 4B for more details.) Asymptomatic carriers are important in sustaining transmission.

G. Epidemiology

Infection can occur in immunized, partially immunized, and unimmunized persons. However, disease is usually less severe in those who are partially or fully immunized. Diphtheria is endemic in many parts of the world, including countries of the Caribbean and Latin America. The incidence of respiratory diphtheria is greatest in the fall and winter, but summer epidemics may occur in warm moist climates in which skin infections are prevalent. During the 1990s, large epidemics of diphtheria, primarily in adolescents and adults, occurred throughout Asia, the Middle East, Turkey, Albania, Russia, and the independent countries of the former Soviet Union. Most life-threatening cases occurred in inadequately immunized persons. In the states of the former Soviet Union (including Russia, the Ukraine, and the Central Asian Republics), over 150,000 cases of and 5,000 deaths due to diphtheria occurred between 1990–1997. In recent epidemics in the former Soviet Union, the case-fatality ratio ranged from 3–23%.

While most cases of diphtheria reported recently in the U.S. were related to importation, enhanced surveillance in a previously endemic area (a Northern Plains Indian community) has revealed ongoing circulation of a toxigenic strain of *C. diphtheriae* first identified in that region in the 1970s. The last known case in Massachusetts occurred in 1994 in an unvaccinated four-year-old child; this was a fatal case, and the source could not be identified. It is estimated that more than 40% of U.S. adults lack protective levels of circulating antitoxin.

In 2004, *C. diphtheria* was isolated from a 60-year-old Massachusetts woman with an unknown vaccination status who had recently traveled to an endemic area. She was diagnosed with a streptococcal throat infection, and it is not clear what role toxigenic diphtheria played in her symptoms. Culture of contacts revealed asymptomatic carriage by another household member, who also had an unknown vaccination history and travel history to the same endemic area in the Caribbean. Both individuals received antibiotics and immunization, and both recovered without sequelae. This incident underscores the need to assess the immunization status of all travelers to diphtheria-endemic areas.

H. Bioterrorist Potential

This pathogen is not considered to be of risk for use in bioterrorism.

Section 2:

REPORTING CRITERIA AND LABORATORY TESTING

A. What to Report to the Massachusetts Department of Public Health (MDPH)

Report any suspect or confirmed case of diphtheria. Laboratory confirmation includes isolation of *C. diphtheriae* from a clinical specimen or histopathologic diagnosis of diphtheria.

Note: See Section 3C for information on how to report a case.

B. Laboratory Testing Services Available

Bacteriological culture and toxigenicity testing of the resulting isolate are essential for confirming diphtheria. Both of these procedures are available at the MDPH State Laboratory Institute (SLI). Clinical specimens for culture should be obtained as soon as possible when diphtheria (involving any site) is suspected, even if treatment with antibiotics has already begun. Close contacts should also be cultured, except in situations where the index of suspicion is low.

Attachment A: Collection of Specimens for Isolation of C. diphtheriae (at the end of this chapter) describes the procedures for collecting specimens for culture and subsequent toxigenicity testing. *Attachment B: Overview of Requirements for Laboratory Testing for Diphtheria* (at the end of this chapter) gives an overview of the diagnostic tests that may be useful in confirming infection, which include polymerase chain reaction (PCR) and serologic testing, available at the Centers for Disease Control and Prevention (CDC).

When submitting clinical specimens to the SLI, use the SLI *Specimen Submission Form* found at the end of this chapter or on the MDPH website at www.mass.gov/dph/bls/generalform.pdf.

Section 3:

REPORTING RESPONSIBILITIES AND CASE INVESTIGATION

A. Purpose of Surveillance and Reporting

- To alert public health authorities to the circulation of *C. diphtheriae* and the possibility of other cases developing in the area, particularly given the large number of susceptible adults.
- To assure early and appropriate treatment with diphtheria antitoxin and antibiotics.
- To obtain necessary laboratory specimens before antibiotic or antitoxin treatment.
- To identify and evaluate contacts, and to provide necessary antimicrobial prophylaxis to prevent further spread of the disease.

B. Laboratory and Health Care Provider Reporting Requirements

Diphtheria is reportable to the local board of health (LBOH). The MDPH requests that health care providers immediately report to the LBOH in the community where the case is diagnosed, all confirmed or suspect cases of diphtheria, as defined by the reporting criteria in Section 2A.

Laboratories performing examinations on any specimens derived from Massachusetts residents that yield evidence of *C. diphtheriae* infection shall immediately report such evidence of infection, directly by phone, to the MDPH Division of Epidemiology and Immunization at (617) 983-6800 or (888) 658-2850.

Due to the potential severity of diphtheria, the MDPH requests that information about any case be immediately reported (24 hours a day/7 days a week) to an epidemiologist at the MDPH Division of Epidemiology and Immunization by calling (617) 983-6800 or (888) 658-2850.

C. Local Board of Health (LBOH) Reporting and Follow-up Responsibilities

Reporting Requirements

MDPH regulations (*105 CMR 300.000*) stipulate that diphtheria is reportable to the LBOH and that each LBOH must report any case of diphtheria or suspect case of diphtheria, as defined by the reporting criteria in Section 2A. A MDPH immunization epidemiologist, in collaboration with the LBOH, will complete an official CDC *Diphtheria Case Report Form* (found at the end of this chapter). Using this form, cases will be reported to the MDPH Bureau of Communicable Disease Control, Office of Integrated Surveillance and Informatics Services (ISIS). Refer to the *Local Board of Health Timeline* at the end of this manual's *Introduction* section for information on prioritization and timeliness requirements of reporting and case investigation.

Case Investigation

1. Due to the potential severity of diphtheria, as well as national surveillance and reporting requirements, the MDPH will take the lead on diphtheria case investigations. This includes filling out the official case report form and making disease control recommendations, in collaboration with the LBOH. MDPH will keep the LBOH informed of all significant developments and will request the assistance of the LBOH as needed.
2. In order to assess the likelihood that a suspect case is a true case prior to laboratory testing, the MDPH and/or other public health staff helping in the investigation should ask about:
   a. Clinical presentation;
   b. Diphtheria immunization history;
   c. Country of origin and length of time in the U.S. (those in the U.S. for a short time are more likely to be susceptible);
   d. History of recent travel (to where and dates);
   e. Whether there were any recent out-of-town visitors (from where and dates);
   f. Whether there was any recent contact with anyone with similar symptoms; and
   g. Risk factors for exposure and transmission (e.g., childcare, school, food handling, health care settings).

3. After the form is completed, the MDPH immunization epidemiologist will forward it to ISIS.
4. Institution of disease control measures is an integral part of case investigation. It is the responsibility of the LBOH to understand, and if necessary, institute the control guidelines listed in Section 4.

Section 4:
CONTROLLING FURTHER SPREAD

This section provides detailed control guidelines that are an integral part of case investigation. The LBOH should familiarize themselves with the information. However, the MDPH will take the lead on implementing control measures, in collaboration with the LBOH.

A. Isolation and Quarantine Requirements *(105 CMR 300.200)*

Minimum Period of Isolation of Patient

Maintain isolation until 2 successive pairs of nose and throat cultures (and cultures of skin lesions in cutaneous diphtheria), obtained ≥24 hours apart and at least 24 hours after completion of antimicrobial therapy, are negative. If there was no antimicrobial therapy, these 2 sequential pairs of cultures shall be taken after symptoms resolve and ≥2 weeks after their onset. If an avirulent (nontoxigenic) strain is documented, isolation is not necessary.

Minimum Period of Quarantine of Contacts

All contacts (both symptomatic and asymptomatic) whose occupations involve handling food must be excluded from that work until 2 successive pairs of nose and throat cultures, obtained ≥2 weeks after completion of antimicrobial prophylaxis (if any) and ≥24 hours apart, are negative. Symptomatic contacts who are not food handlers shall be considered the same as a case until their culture results are negative and they are cleared by the MDPH. Asymptomatic contacts that are not food handlers must be on appropriate antibiotics and personal surveillance.

These requirements may be extended to other contacts that work in high-risk transmission settings, as determined by the MDPH.

B. Management of a Case and Protection of Contacts of a Case

The management of cases and contacts described in this section is divided into three categories: 1) case and symptomatic close contacts; 2) asymptomatic close contacts; and 3) nonsignificant contacts. It is important to follow the sequence of actions as administration of antibiotics, diphtheria antitoxin (DAT), and diphtheria toxoids will interfere with the interpretation of diagnostic testing. *Attachment C: Algorithm for Diagnosis, Treatment, and Follow-up of Suspect Diphtheria Cases and Infected Contacts* (found at the end of this chapter) presents these recommendations in diagram form.

Definition of Close Contact

Close contacts are defined as persons who sleep in the same house or who share food, drink, or eating/drinking utensils with the case, as well as health care workers in contact with the case's oral or respiratory secretions.

Contacts that were in brief contact with the case but who do not meet the definition for close contact are not considered significant contacts.

Case(s) and Symptomatic Close Contacts

Symptomatic close contacts are managed the same as cases until cultures (as described above) are negative and the MDPH evaluates the symptoms and determines whether or not they meet the clinical case definition and should continue to be managed like a case.

1. Isolate the confirmed or suspect respiratory case on droplet precautions.
2. Obtain specimens for *C. diphtheriae* culture as described in *Attachment A: Collection of Specimens for Isolation of C. diphtheriae* (found at the end of this chapter). If antibiotics have been started, it is useful to collect specimens for PCR and serology as well (described in *Attachment B: Overview of Requirements for Laboratory Testing for Diphtheria,* found at the end of this chapter). Blood for serology should be collected before administration of DAT or diphtheria toxoid.
3. Cases and symptomatic close contacts should also be evaluated for initiation of therapy with DAT. DAT can be obtained through an Investigational New Drug (IND) protocol via the CDC. Health care providers treating a suspect case of diphtheria can contact the diphtheria duty officer directly at the CDC Bacterial Vaccine-Preventable Disease Branch, Epidemiology and Surveillance Division, National Immunization Program (NIP) in Atlanta at (404) 639-8257 from 8 A.M. to 4:30 P.M. or via the CDC Emergency Operations Center at (770) 488-7100 at all other times. The MDPH should be notified immediately if DAT is requested from the CDC. (See *Attachment D: Important Telephone Contacts for Diphtheria Control* at the end of this chapter for important telephone numbers.) Remember, if serology specimens are to be collected, this should be done ***before*** administration of DAT.
4. Initiate antimicrobial treatment for cases and symptomatic close contacts as follows (preferably after collection of specimens):
    a. Erythromycin parenterally (40–50 mg/kg/day, maximum 2 g/day) until patient can swallow comfortably, at which point either oral erythromycin in 4 divided doses or oral penicillin V, 125–250 mg 4 times a day, may be substituted for a total treatment period of 14 days; or
    b. Aqueous crystalline penicillin G intramuscularly (100,000–150,000 U/kg/day, in 4 divided doses) daily for 14 days; or aqueous procaine penicillin intramuscularly (25,000–50,000 U/kg, maximum 1.2 million U, in 2 divided doses for children and 1.2 million U for adults) daily for 14 days.
5. Continue with droplet precautions until two cultures from both the nose and the throat are negative for toxigenic *C. diphtheriae*. Specimens for these cultures should be taken at least 24 hours after cessation of antimicrobial therapy and ≥24 hours apart. If cases or asymptomatic contacts did not receive antimicrobial therapy, the cultures should be taken after symptoms resolve, ≥2 weeks after their onset and ≥24 hours apart. Place the cutaneous diphtheria cases on contact precautions until two cultures of the skin lesions are negative.
6. Cases and symptomatic close contacts who are not up-to-date for diphtheria toxoid-containing vaccines should be immunized with a diphtheria toxoid-containing preparation appropriate for age during convalescence, as disease does not necessarily confer immunity. (Please refer to *Attachment E: Schedules for Routine and Accelerated Immunization with Diphtheria and Tetanus-Containing Vaccines* at the end of this chapter for more information.) Remember, if serum is to be collected, do this before vaccinating.

General guidelines for assessing diphtheria toxoid vaccination status are as outlined:

a. If <3 doses or unknown, administer a dose of diphtheria toxoid (DTaP, DT, Td, or Tdap as appropriate), and complete primary series according to schedule.

b. If ≥3 doses and last dose was >5 years ago, administer a booster dose of diphtheria toxoid.

c. If ≥3 doses and last dose was <5 years ago, children needing their 4th primary dose or booster dose should be vaccinated; otherwise vaccination is not required.

For additional information, please refer to *Attachment E: Schedules for Routine and Accelerated Immunization with Diphtheria and Tetanus-Containing Vaccines,* found at the end of this chapter.

7. Close contacts should be monitored daily for symptoms for at least seven days after their last exposure. Active surveillance for suspect cases in the affected settings should take place for at least two incubation periods (ten days).

Asymptomatic Close Contacts

1. Where diphtheria is confirmed or highly suspected in the case, all asymptomatic close contacts should have cultures collected as described in *Attachment A: Collection of Specimens for Isolation of C. diphtheriae* (found at the end of this chapter).
2. Administer prophylactic antibiotic therapy irrespective of immunization status. Close contacts (regardless of their culture result or immunization status) should begin antibiotic prophylaxis with oral erythromycin (40–50 mg/kg/day for 10 days, maximum 2 g/day, for children and 1 g/day for adults). A single IM dose of benzathine penicillin G (600,000 U for persons <6 years of age and 1,200,000 U for persons ≥6 years of age) is an alternative. (The lower dose of penicillin is for patients weighing <30 kg.)
3. Obtain nasal and throat specimens for culture.
   a. If asymptomatic close contacts are culture-positive, they will need to repeat nasopharyngeal and throat cultures ≥2 weeks after antibiotics have been discontinued and ≥24 hours apart. If both sets of cultures are negative, the individual is considered free of infection. If any of the repeat cultures are positive, an additional ten-day course of oral erythromycin should be administered and follow-up cultures will need to be repeated as described above.
   b. If an asymptomatic contact has not received antibiotics, 2 successive pairs of nose and throat cultures taken ≥24 hours apart are needed. If any of the repeat cultures are positive, a ten-day course of oral erythromycin should be given, and the cultures should be repeated as described above.
4. Assess close contacts for diphtheria toxoid vaccination status and whether they are up-to-date according to the recommended schedule for age. If not, they should be immunized with a diphtheria toxoid-containing preparation appropriate for age. (Please see *Attachment E: Schedules for Routine and Accelerated Immunization with Diphtheria and Tetanus-Containing Vaccines* at the end of this chapter.)

   General guidelines for assessing diphtheria toxoid vaccination status are as outlined:

   a. If <3 doses or unknown, administer a dose of diphtheria toxoid (DTaP, DT, Td, or Tdap as appropriate), and complete primary series according to schedule.

   b. If ≥3 doses and last dose was >5 years ago, administer a booster dose of diphtheria toxoid.

   c. If ≥3 doses and last dose was <5 years ago, children needing their 4th primary dose or booster dose should be vaccinated; otherwise vaccination is not required.

5. Close contacts should be monitored daily for symptoms for at least seven days after their last exposure. Active surveillance for suspect cases in the affected settings should take place for at least two incubation periods (ten days).

Non-Significant Contacts

Contacts who do not sleep in the same house as the case, do not share food, drink, or eating/drinking utensils with the case, and are not health care workers in contact with the case's oral or respiratory secretions should be immunized with the appropriate diphtheria-toxoid-containing preparation, as described in *Attachment E: Schedules for Routine and Accelerated Immunization with Diphtheria and Tetanus-Containing Vaccines* (found at the end of this chapter). They do not need to be cultured or placed on antibiotic prophylaxis.

C. Preventive Measures

Routine vaccination is the best preventive measure against diphtheria. Diphtheria toxoid and DTaP vaccine should be used in persons <7 years of age, whereas Td vaccine is the preferred preparation for persons ≥7 years of age. Tables outlining the routine and accelerated schedules for these vaccines can be found in *Attachment E: Schedules for Routine and Accelerated Immunization with Diphtheria and Tetanus-Containing Vaccines* (found at the end of this chapter).

- All patients, particularly those who are foreign-born, should have their immunization status assessed to ensure they have received the three-dose primary series of a diphtheria toxoid containing vaccine. Booster doses of Td should then be administered beginning at age 11–12 years and every 10 years thereafter. (Tdap vaccine may also be administered as a single dose to adolescents and adults.)
- All travelers, particularly those to diphtheria endemic areas, should be assessed prior to departure and should receive a primary series or booster if indicated. Children with any incomplete schedule and adults with fewer than three doses should receive as many doses as possible prior to departure using the accelerated schedules in *Attachment E: Schedules for Routine and Accelerated Immunization with Diphtheria and Tetanus-Containing Vaccines* (found at the end of this chapter).
- Good personal hygiene (i.e., proper handwashing, disposal of used tissues, not sharing eating utensils, etc.) is also important in prevention.
- All children <7 years of age should receive a routine series of 5 doses of tetanus and diphtheria toxoid-containing vaccine at ages 2, 4, 6, 15–18 months, and 4–6 years.
- All unvaccinated individuals ≥7 years of age should receive 3 doses of Td vaccine. The 2nd dose is usually given 1–2 months after the 1st dose, and the 3rd dose is given 6 months after the 2nd dose.

Please refer to the most current versions of the MDPH's *Immunization Guidelines* and *Massachusetts Immunization Program-State Supplied Vaccines and Patient Eligibility Criteria* for details about DTaP/DT/Td vaccination, the recommended schedule, who should and should not get the vaccine, and who is eligible to receive state-supplied vaccine. These, as well as other relevant resources, are available through the MDPH Division of Epidemiology and Immunization at (617) 983-6800 or (888) 658-2850.

Note: For more information regarding international travel and diphtheria, contact the CDC's Traveler's Health Office at (877) 394-8747 or at www.cdc.gov/travel.

ADDITIONAL INFORMATION

The following is the CDC surveillance case definition for diphtheria. It is provided for your information only and should not affect the investigating or reporting of a case that fulfills the criteria in Section 2A of this chapter. (The CDC and the MDPH use the CDC case definitions to maintain uniform standards for national reporting.) For reporting to the MDPH, always use the criteria outlined in Section 2A.

Note: The most up-to-date CDC case definitions are available on the CDC website at www.cdc.gov/epo/dphsi/casedef/case_definitions.htm.

Clinical Description

An upper respiratory tract illness characterized by sore throat, low-grade fever, and an adherent membrane of the tonsil(s), pharynx, and/or nose.

Laboratory Criteria for Diagnosis

Isolation of *C. diphtheriae* from a clinical specimen or histopathologic diagnosis of diphtheria.

Case Classification

Probable	A skin lesion evolving during a period of 2–6 days from a papule, through a vesicular stage, to a depressed black eschar.
Confirmed	A clinically compatible case that is either laboratory-confirmed or epidemiologically linked to a laboratory-confirmed case.

Respiratory disease caused by non-toxigenic *C. diphtheriae* should be reported as diphtheria. Cutaneous diphtheria should not be reported. All diphtheria isolates, regardless of association with disease, should be sent through the MDPH to the Diphtheria Laboratory, National Center for Infectious Diseases, CDC. See *Attachment A: Collection of Specimens for Isolation of C. diphtheriae* (found at the end of this chapter) for more information.

REFERENCES

American Academy of Pediatrics. [Diphtheria.] In: Pickering, L.K., ed. *Red Book 2003: Report of the Committee on Infectious Diseases, 26th Edition*. Elk Grove Village, IL, Academy of Pediatrics; 2003: 263–266.

CDC. Case Definitions for Infectious Conditions Under Public Health Surveillance. *MMWR*. 1997; 46(RR-10).

CDC. *Epidemiology and Prevention of Vaccine-Preventable Diseases: The Pink Book, 8th Edition*. CDC, January 2004.

CDC. Health Information for International Travel. 2003.

CDC. *Manual for the Surveillance of Vaccine-Preventable Diseases*. CDC, 2002.

Heymann D., ed. *Control of Communicable Diseases Manual, 18th Edition*. Washington, DC, American Public Health Association, 2004.

MDPH. *Regulation 105 CMR 300.000: Reportable Diseases, Surveillance, and Isolation and Quarantine Requirements.* MDPH, Promulgated November 4, 2005.

ATTACHMENTS

Attachment A: Collection of Specimens for Isolation of C. diphtheriae

Attachment B: Overview of Requirements for Laboratory Testing for Diphtheria

Attachment C: Algorithm for Diagnosis, Treatment, and Follow-Up of Suspect Diphtheria Cases and Infected Contacts

Attachment D: Important Telephone Contacts for Diphtheria Control

Attachment E: Schedules for Routine and Accelerated Immunization with Diphtheria and Tetanus-Containing Vaccines

Attachment A

Collection of Specimens for Isolation of *C. diphtheriae*

Clinical specimens for culture should be obtained as soon as possible when diphtheria (involving any site) is suspected, even if treatment with antibiotics has already begun. Unless the index of suspicion is low, close contacts of suspect cases should have specimen for culture taken from the nose and the throat. (Culture of *C. diphtheriae* from close contacts may confirm the diagnosis of the case, even if the patient's culture is negative.) Use a dry, sterile polyester swab.

Throat Swabs	1. Pharynx should be clearly visible and well-illuminated. 2. Depress tongue with an applicator and swab the throat without touching the tongue or inside of the cheek. 3. Rub vigorously over any membrane, white spots, or inflamed areas; slight pressure with a rotating movement must be applied to the swab. 4. If any membrane is present, lift the edge and swab beneath it to reach the deeply located organisms. A portion of the membrane may also be submitted for testing.
Nasopharyngeal Specimens	1. Insert the swab into the nose through one nostril beyond the anterior nares. 2. Gently introduce the swab along the floor of the nasal cavity, under the middle turbinate until the pharyngeal wall is reached. Force must not be used to overcome any obstruction. Leave swab in place for ten seconds. This procedure may induce coughing and tearing. Remove the swab slowly. For PCR, specimens should be taken at the same time as those for culturing. Place swabs in sterile, dry tube or vial. 3. Ship immediately at +4°C (with cold packs in a sterile container or in silica gel sachets), so that specimen arrives at the laboratory as soon as possible after collection.
Skin Diphtheria and Other Lesions	1. Lesions should be cleansed with sterile, normal saline, and crusted material should be removed. 2. Press the swab firmly into the lesion.

Place swabs in a culturette swab transport system. If transport time is anticipated to be <24 hours, Amies or Modified Stuart's medium is recommended. If transport time is to be ≥24 hours, silica gel is recommended. Send specimen with the SLI *Specimen Submission Form* (found at the end of this chapter or on the MDPH website at www.mass.gov/dph/bls/generalform.pdf) to the SLI.

Call a MDPH immunization epidemiologist at (617) 983-6800 or (888) 658-2850 to arrange for specimen submission and to notify the SLI bacteriologist that specimens for diphtheria culture are on the way, since isolation of *C. diphtheriae* requires special tellurite-containing media.

If *C. diphtheriae* is isolated, regardless of association with disease, MDPH staff will arrange for shipment of isolates to the Diphtheria Laboratory, National Center for Infectious Diseases, CDC, as directed by the CDC.

Updated March 2005

Attachment B

Overview of Requirements for Laboratory Testing for Diphtheria*

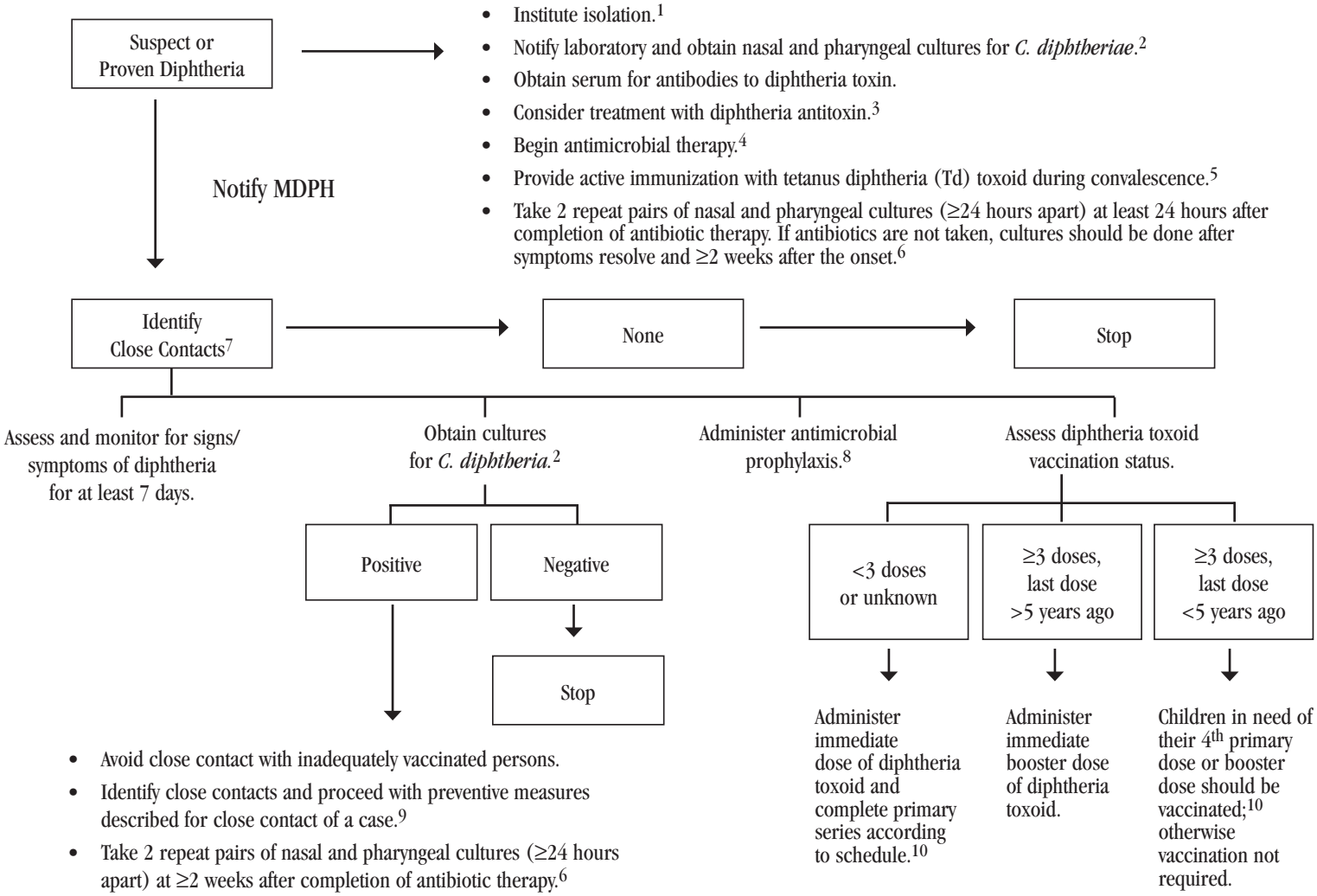
Test Name	Specimens to Take	Timing for Specimen Collection	Transport Requirements	Collection & Notification Requirements	Notes
Culture	• Swabs of nose, throat, and membrane (or other infected body site) of case. • Swabs of nose and throat of close contacts.	As soon as possible, when diphtheria is suspected.	<24 hours: Amies or modified Stuart's medium. ≥24 hours: Silica gel sachets.	Physicians or laboratories: Call SLI at (617) 983-6607 and MDPH Division of Epidemiology and Immunization at (617) 983-6800 or (888) 658-2850 regarding suspected case. MDPH may call CDC Diphtheria Laboratory at (404) 639-1730 or (404) 639-4057.	Available at SLI and elsewhere. Alert laboratory that diphtheria is suspected to ensure that tellurite-containing media is used. After isolation, biotype (strain) and toxigenicity can be determined.
PCR	Swabs (as above), or pieces of membrane or biopsy tissue of case.	As soon as possible, when diphtheria is suspected.	Silica gel sachet, or a sterile dry container at 4°C.	Contact as above.	Available only at CDC. Alert laboratory that diphtheria is suspected so that specific PCR assay is used. Can detect non-viable organisms and toxin gene. Provides supportive evidence for, but not confirmation of, diagnosis.
Toxigenicity Testing (Elek Test)	Isolate from culture of case (as above).	After *C. diphtheriae* has been isolated.	Transport medium such as Amies medium or silica gel sachets.	Contact as above.	Available at SLI, CDC, and elsewhere.
Serology (Antibodies to Diphtheria Toxin)	Serum from case.	Before administration of antitoxin or vaccine, collect paired sera taken 2–3 weeks apart.	Frozen (-20°C).		Not available at CDC or SLI. If acute antibody levels are low, diphtheria can't be ruled out; if acute levels are high, diphtheria is unlikely to be cause of illness.

*Adapted and updated from www.cdc.gov/nip/publications/surv-manual/chpt19_lab_support.pdf.

Please note: When submitting clinical specimens to the SLI, use the SLI *Specimen Submission Form* found at the end of this chapter.

Attachment C

Algorithm for Diagnosis, Treatment, and Follow-up of Suspect Diphtheria Cases and Infected Contacts



1 Maintain isolation until elimination of the organism is demonstrated by negative cultures of 2 samples obtained at least 24 hours apart and taken ≥24 hours after completion of antimicrobial therapy. If antibiotic therapy is not taken, cultures should be done after symptoms resolve and it is ≥2 weeks since their onset.

2 Both nasal and pharyngeal swabs should be obtained for culture.

3 If equine diphtheria antitoxin (DAT) is needed, it can be obtained through an Investigational New Drug (IND) protocol from the CDC. Before administration, patients should be tested for sensitivity to horse serum, and if necessary, they should be desensitized. The recommended dosage and route of administration depend on the extent and duration of disease. Detailed recommendations can be obtained from the package insert and other publications.

4 Antimicrobial therapy is not a substitute for antitoxin treatment. Antimicrobials: 1) intramuscular procaine penicillin G (25,000–50,000 units/kg/day maximum 1.2 million units in 2 divided doses for children, and 1.2 million units for adults) for 14 days; 2) aqueous crystalline penicillin G intramuscularly (100,000–150,000 units/kg/day, in 4 divided doses) for 14 days; or 3) parenteral erythromycin (40–50 mg/kg/day, maximum 2 g/day) have been recommended until the patient can swallow comfortably, at which point oral erythromycin in 4 divided doses or oral penicillin V (125–250 mg 4 times per day) may be substituted for a recommended total treatment period of 14 days.

5 Vaccination with Td toxoid is required because clinical diphtheria does not necessarily confer immunity.

6 Persons who continue to harbor the organism after treatment with either penicillin or erythromycin should receive an additional ten-day course of oral erythromycin and should submit samples for follow-up cultures.

7 Close contacts include persons who sleep in the same house or who share food, drink, or eating/drinking utensils with the case, as well as health care workers exposed to oral or respiratory secretions of a case-patient.

8 A single dose of intramuscular benzathine penicillin G (600,000 units for persons <6 years of age and 1.2 million units for persons ≥6 years of age) or oral erythromycin (40–50 mg/kg/day for 10 days, maximum 2 g/day, for children; and 1 g/d for adults) has been recommended.

9 Preventive measures may be extended to close contacts of carriers but should be considered a lower priority than control measure for contacts of each case.

10 Refer to published recommendations for the schedule for routine administration of DTaP.

Adapted and updated from: Farizo K.M., Strebel P.M., Chen R.T., et al. Fatal Respiratory Disease Due to *Corynebacterium diphtheriae*: Case Report and Review of Guidelines for Management, Investigation, and Control. *Clin Infect Dis*. 1993; 16: 59–68.

Attachment D

Important Telephone Contacts for Diphtheria Control

MDPH State Laboratory Institute (SLI) 305 South Street Jamaica Plain, MA 02130	
Massachusetts Department of Public Health (MDPH) Division of Epidemiology and Immunization Immunization epidemiologist-on-call	(617) 983-6800 or (888) 658-2850
Bacteriology Laboratory (Bacteriologists available Monday–Friday, 8:00 A.M. – 5:00 P.M.)	(617) 983-6600
Centers for Disease Control and Prevention (CDC) Bacterial Vaccine-Preventable Disease Branch Epidemiology and Surveillance Division (MS E-61) National Immunization Program (NIP)	(404) 639-8257
Epidemic Investigations Laboratory (MS D-11) **National Center for Infectious Diseases (NCID)** Dr. Patty Wilkins Dr. Pam Cassiday	(404) 639-3297 or (404) 639-1231
For Diphtheria Antitoxin (DAT), please contact: CDC Diphtheria Duty Officer through CDC Emergency Operations Center (EOC) Centers for Disease Control and Prevention Emergency Operations Center (MS D-75) 1600 Clifton Road, NE Atlanta, GA 30333 Ask for Diphtheria Duty Officer on-call to be paged (available days, nights, weekends, and holidays). Please remember to also immediately notify the MDPH Division of Epidemiology and Immunization at (617) 983-6800 or (888) 658-2850, 24 hours a day/7 days a week, if DAT is requested.	(770) 488-7100

Attachment E

Schedules for Routine and Accelerated Immunization with Diphtheria and Tetanus-Containing Vaccines

DTaP Schedule for Children <7 Years of Age[1]

Dose	Vaccine	Recommended Age	Accelerated Schedule
1	DTaP	2 months	≥6 weeks of age
2	DTaP	4 months	≥4 weeks after 1st dose
3	DTaP	6 months	≥4 weeks after 2nd dose
4[2]	DTaP	15–18 months	≥6 months after 3rd dose
5[2,3]	DTaP	4–6 years	≥6 months after 4th dose
Additional Boosters	Td	11–12 years of age, if ≥5 years since 5th dose, then every 10 years	1st booster ≥5 years after the 5th dose, then every 10 years

1 DTaP and DT should not be given to individuals ≥7 years of age.

2 The 4th dose of DTaP may be administered as early as 12 months of age, provided 6 months have elapsed since the 3rd dose and the child is unlikely to return at age 15–18 months.

3 The 5th dose of DTaP is not necessary if the 4th dose was given on or after the 4th birthday.

Td Schedule for Individuals ≥7 Years of Age[1]

Dose	Recommended Schedule	Accelerated Schedule
1	First visit	--
2	1–2 months after 1st dose	≥4 weeks after 1st dose
3	≥6 months after 2nd dose	≥6 months after 2nd dose
Additional Boosters	At 11–12 years of age and no later than 16 years of age (if it has been ≥5 years since last dose), then every 10 years throughout life	--

1 Td should not be given to individuals <7 years of age.

FORMS & WORKSHEETS

Diphtheria

Diphtheria

REPORT IMMEDIATELY

LBOH Action Steps

This form does not need to be submitted to the MDPH with the case report form. It is for LBOH use and is meant as a quick-reference guide to diphtheria case investigation activities.

LBOH staff should follow these steps when diphtheria is suspected or confirmed in the community. For more detailed information, including disease epidemiology, reporting, case investigation, and follow-up, refer to the preceding chapter.

Note: Due to the potential severity of diphtheria as well as national surveillance and reporting requirements, MDPH epidemiologists will usually take the lead on diphtheria investigation. This includes filling out the official case report form and making disease control recommendations, in collaboration with the LBOH. MDPH epidemiologists will keep the LBOH informed of all significant developments and will request the assistance of the LBOH as needed.

Reporting Responsibilities

- ❑ Immediately notify the MDPH Division of Epidemiology and Immunization, at (617) 983-6800 or (888) 658-2850, to report any confirmed or suspect case(s) of diphtheria.

Case Investigation

- ❑ Work with the MDPH to ensure that appropriate clinical specimens are collected and submitted to the SLI for confirmation.
- ❑ Work with the MDPH to obtain the information necessary for completion of the case report form, including source of exposure, clinical information, vaccination history, laboratory results, and source of infection. (The MDPH will complete the form and submit to the MDPH Bureau of Communicable Disease Control, Office of Integrated Surveillance and Informatics Services [ISIS].)
- ❑ Determine if any close contacts have occupations that involve handling food.
- ❑ Since diphtheria disease does not result in immunity, a diphtheria-containing vaccine (DTaP, DT, Td, or Tdap) should be administered to the patient during convalescence.

Prevention and Control

- ❑ Work with the MDPH to institute isolation and quarantine requirements (*105 CMR 300.200*) and other control measures, as they apply to a particular case.
- ❑ Determine if any close contacts are susceptible (e.g., those without documentation of vaccination, including those with medical or religious exemptions).
- ❑ Vaccinate susceptible individuals with diphtheria-containing vaccine (DTaP, DT, Td, or Tdap).

Diphtheria

- ❑ For all highly suspect and confirmed cases:
  - ❑ Ensure all close contacts whose occupations involve handling food are appropriately tested, receive antibiotics, and are excluded from work until cultures are negative.
  - ❑ Close contacts who are not food handlers should be cultured and placed on appropriate antibiotics.
- ❑ Conduct surveillance for two incubation periods.

Managing Diphtheria in Schools and Other Institutions

In addition to the prevention and control measures described above:

- ❑ Determine if there are any close contacts in these settings.
- ❑ Culture contacts and place on appropriate antibiotics.
- ❑ Implement surveillance for new cases.
- ❑ Notify and educate staff, students, and/or patients.
- ❑ Test and exclude symptomatic individuals.
- ❑ Isolate remaining susceptible contacts.

Managing Diphtheria in Health Care Settings

In addition to the prevention and control measures described above:

- ❑ Notify infection control or employee health of confirmed or suspect case(s) in institution.